ORIGINAL INVESTIGATION

Effect of Vitamin E and Beta Carotene on the Incidence of Primary Nonfatal Myocardial Infarction and Fatal Coronary Heart Disease

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Background: Oxidized low-density lipoprotein is involved in the pathogenesis of atherosclerosis. In epidemiological studies antioxidants have been inversely related with coronary heart disease. Findings from controlled trials are inconclusive.

Methods: We studied the primary preventive effect of vitamin E (alpha tocopherol) and beta carotene supplementation on major coronary events in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, a controlled trial undertaken primarily to examine the effects of these agents on cancer. A total of 27 271 Finnish male smokers aged 50 to 69 years with no history of myocardial infarction were randomly assigned to receive vitamin E (50 mg), beta carotene (20 mg), both agents, or placebo daily for 5 to 8 years (median, 6.1 years). The end point was the first major coronary event, either nonfatal myocardial infarction (surviving at least 28 days; n=1204) or fatal coronary heart disease (n=907).

Results: The incidence of primary major coronary events decreased 4% (95% confidence interval, −12% to 4%) among recipients of vitamin E and increased 1% (95% confidence interval, −7% to 10%) among recipients of beta carotene compared with the respective nonrecipients. Neither agent affected the incidence of nonfatal myocardial infarction. Supplementation with vitamin E decreased the incidence of fatal coronary heart disease by 8% (95% confidence interval, −19% to 5%), but beta carotene had no effect on this end point.

Conclusions: Supplementation with a small dose of vitamin E has only marginal effect on the incidence of fatal coronary heart disease in male smokers with no history of myocardial infarction, but no influence on nonfatal myocardial infarction. Supplementation with beta carotene has no primary preventive effect on major coronary events.

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THE INVOLVEMENT of oxidized low-density lipoprotein in the pathogenesis of atherosclerosis has raised interest in antioxidants as possible preventive agents of cardiovascular disease.[1,2] Despite strong experimental evidence, the preventive effect of antioxidant supplementation on cardiovascular events in humans is unproven. In observational studies, use of vitamin E (alpha tocopherol) supplements has been associated with decreased risk for subsequent coronary events.[3,4] Large-scale randomized trials with beta carotene supplementation have shown either no reduction in cardiovascular diseases[5] or even an increase in cardiovascular mortality.[6,7] In a placebo-controlled trial, vitamin E treatment significantly reduced the risk of nonfatal myocardial infarction in patients with coronary disease.[8]

The initial results of The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study)[6] indicated that there were fewer deaths due to coronary heart disease among subjects who received vitamin E supplements compared with those who did not, but more deaths among subjects who received beta carotene supplements compared with those who did not. This report expands these findings by presenting the effect of vitamin E and beta carotene on the incidences of primary nonfatal myocardial infarction and fatal coronary heart disease.

RESULTS

At study entry there were no differences in the risk factors of coronary heart disease between the intervention groups (**Table 1**). Similarly, the total intakes of energy and fat and different fatty acids were evenly distributed between the groups (data not shown).

About 20% of the subjects stopped smoking during their active participation in the study, and the proportion was similar in all 4 intervention groups. Sys-

PATIENTS AND METHODS

STUDY DESIGN

The rationale, design, and methods of The ATBC Study have been described in detail elsewhere.[9] The study was a randomized, double-blind, placebo-controlled trial undertaken primarily to determine whether supplementation with vitamin E, beta carotene, or both would reduce the incidence of lung cancer and other cancers. Participants were male smokers (≥5 cigarettes per day at entry) aged 50 to 69 years who were recruited from the total male population of this age group in southwestern Finland (N=290 406). Their smoking status and willingness to participate were ascertained in a postal survey. Final eligibility was assessed during 2 baseline visits, after which the participants (n=29 133) were randomly assigned to 1 of 4 supplementation regimens: vitamin E, 50 mg/d; vitamin E, 50 mg/d, plus beta carotene, 20 mg/d; beta carotene, 20 mg/d; or placebo. Exclusion criteria were proven malignancy, severe angina pectoris (angina from walking on level ground), chronic renal insufficiency, cirrhosis of the liver, alcoholism, other medical problems that might limit participation, use of anticoagulants, or use of supplements of vitamin E, vitamin A, or beta carotene in excess of predefined doses.

Randomization was performed in blocks of 8 within each of the 14 local study centers. Participants and all study staff remained blinded to the participants' intervention assignments throughout the trial.

At baseline 1862 men reported a history of myocardial infarction diagnosed by a physician, leaving 27 271 men for this study of primary prevention of myocardial infarction. Of them, 6820 men had been randomized to receive vitamin E; 6781 to receive vitamin E and beta carotene; 6821 to receive beta carotene; and 6849 to receive placebo. Thus, half of the participants received vitamin E (n=13 601) and half did not (n=13 670). Similarly, half received beta carotene (n=13 602) and half did not (n=13 669). Participants were recruited from 1985 through 1988 and supplementation continued for 5 to 8 years (median, 6.1 years) until trial closure (April 30, 1993).

The ATBC Study was approved by the review boards of the participating institutions, and all subjects provided written informed consent before randomization. A data and safety monitoring committee convened twice annually throughout the study to review its progress and integrity and to evaluate data relevant to safety and efficacy.

BASELINE AND FOLLOW-UP MEASURES

Fourteen local study centers administered by specially trained registered nurses were set up for the ATBC Study visits. At the first baseline visit the men returned a questionnaire on general background characteristics and medical and smoking histories, which were sent to them by mail. The questionnaire was reviewed together with a study nurse. Height, weight, and blood pressure were measured in a standardized manner. A blood sample was drawn and serum stored at −70°C. Two weeks later during their second baseline visit, the men returned a detailed dietary questionnaire that they reviewed together with a nurse.

After randomization the participants made 3 follow-up visits annually. During these visits the men were asked about their health (illnesses and symptoms including self-perceived skin yellowing) and smoking habits since the last visit. Once a year blood pressure and weight were measured. The participants received a new supply of study capsules at each follow-up visit. The capsules were packaged in coded blister-pack wallets in calendar format and contained the study agents in the form of synthetic *dl*-alpha tocopheryl acetate (50% powder) and synthetic beta carotene (10% water-soluble beadlets). Participants took 1 capsule daily and compliance was assessed by counts of the remaining capsules at each visit. A follow-up blood sample was drawn after 3 years' supplementation and serum stored at −70°C.

Serum levels of total and high-density lipoprotein cholesterol, alpha tocopherol, and beta carotene were analyzed from both baseline and 3-year follow-up serum samples. Cholesterol concentrations were determined enzymatically (CHOD-PAP method, Boehringer Mannheim, Mannheim, Germany). High-density lipoprotein cholesterol was measured after precipitation of very low-density and low-density lipoproteins with dextran sulfate sodium and magnesium chloride. Determinations of alpha tocopherol and beta carotene levels were done by high-performance liquid chromatography.[10]

Continued on next page

tolic and diastolic blood pressure, levels of total and high-density lipoprotein cholesterol, and body mass index remained similar in the 4 intervention groups throughout the study.

Dropout rates prior to major coronary event or trial closure were similar in the 4 intervention groups, ranging from 26.4% to 27.2%, with more than half of the dropouts occurring during the first 2 years. Likewise, capsule compliance was similar across the groups; median percentage of capsules taken was 99.0% in each group.

There were 2111 primary major coronary events during the trial follow-up of 156 178 person-years, including 1204 cases of nonfatal myocardial infarction and 907 cases of fatal coronary heart disease.

Incidences of major coronary events in the intervention groups ranged from 13.2 to 14.0 per 1000 person-years. The relative risks in the active intervention groups compared with the placebo group were 0.98 for the vitamin E group, 0.97 for the vitamin E plus beta carotene group, and 1.03 for the beta carotene group (**Table 2**). The small differences between the groups were not statistically significant. Similarly, the incidences of both nonfatal myocardial infarction and fatal coronary heart disease differed little between the intervention groups. The relative risks of these end points in the active intervention groups compared with the placebo group ranged from 0.90 to 1.06 (Table 2). These differences were also not significant. There was no evidence of interaction between the vitamin E and beta carotene supplements in their effect on major coronary events ($P=.64$), nonfatal myocardial infarction ($P=.32$), or fatal coronary heart disease ($P=.67$).

In the 2×2 factorial comparison, recipients of vitamin E had a 4% reduction (95% CI, −12% to 4%) in the

END POINTS

The end points of this study were primary nonfatal acute myocardial infarction and death from coronary heart disease, collectively called major coronary events. Only the first event after randomization was registered as an end point. End points were identified from national registers. In Finland, all hospitalizations are registered in the Hospital Discharge Register and all deaths in the Register of Causes of Death. Both registers use the codes of the *International Classification of Diseases*,[11] the eighth edition of which was used up to the end of 1986, and *International Classification of Diseases, Ninth Revision*[12] thereafter.

Record linkage to the registers was done using the unique personal identity number. The first acute myocardial infarction (code 410) after randomization was searched for in the Hospital Discharge Register. When a case was found, survival for more than 28 days from the beginning of the attack was checked using the Register of Causes of Death, and survivors were considered cases of nonfatal myocardial infarction. Those who died within 28 days were considered cases of deaths due to coronary disease together with those fatal cases identified from the Register of Causes of Death with the underlying cause of death coded as 410-414. Register follow-up continued throughout the ATBC Study; thus, cases could also be identified among those who discontinued participation. Validity of the diagnoses of the major coronary events in the registers has been evaluated and found to be good, since 94% of the cases of a random sample (n=408) retained either definite or possible myocardial infarction in a review of clinical and autopsy data, according to the FINMONICA criteria, the criteria of the Finnish participation in the World Health Organization MONICA project.[13]

STATISTICAL METHODS

The incidences of major coronary events (nonfatal myocardial infarction and fatal coronary heart disease) were assessed per 1000 person-years of follow-up in the 4 intervention groups, and the unadjusted relative risks were calculated in the active intervention groups compared with the placebo group. Poisson regression model was used for testing the estimated relative risks and for computing the confidence intervals (CIs). Kaplan-Meier survival curves and 2-sided *P* values derived from the unweighted log-rank statistic were assessed for both supplements: vitamin E compared with no vitamin E, and beta carotene compared with no beta carotene. The effect of supplementation is expressed as the percentage change in the incidence of major coronary events.

Interaction between the effects of vitamin E and beta carotene was tested using the likelihood ratio test in Cox proportional hazards regression. Effect modification by baseline factors (age, number of cigarettes daily, years of smoking, levels of total and high-density lipoprotein cholesterol, systolic and diastolic blood pressure, daily alcohol consumption, body mass index [measured as the weight in kilograms divided by the square of the height in meters], leisure-time physical activity, history of angina pectoris and diabetes, dietary intake, and serum concentrations of alpha tocopherol and beta carotene) was tested similarly, with continuous factors divided into tertiles. Additionally, linear trend in relative risks across baseline factor classes was tested against no interaction.

When studying the effects of duration of the supplementation and self-perceived skin yellowing on the risk of primary major coronary events, the intention-to-treat principle had to be abandoned due to subjects discontinuing study participation. To account for possible differences in those discontinuing participation between the groups, the relative risks were adjusted for the risk factors of coronary heart disease by Cox regression. The effect of the serum concentration of alpha tocopherol and beta carotene during respective supplementation was studied similarly, adjusting additionally for the respective baseline concentration. This analysis was done both in the quintiles of the serum concentration at 3 years and in the quintiles of the change in concentration from baseline to 3 years, and it included only those subjects who had a follow-up serum sample taken at 3 years and had not yet experienced a major coronary event.

The association of tertiles of baseline intakes and serum levels of vitamin E and beta carotene with the incidence of major coronary events was calculated by Cox regression in the placebo group.

incidence of primary major coronary events compared with men who did not receive vitamin E (**Figure**). The decrease was mostly due to an 8% reduction (95% CI, −19% to 5%) in fatal coronary heart disease, whereas no effect on nonfatal myocardial infarction was observed (−1%; 95% CI, −12% to 10%). The incidences of major coronary events (nonfatal myocardial infarction and fatal coronary heart disease) were similar among men who received beta carotene and those who did not: difference, 1% (95% CI, −7% to 10%), 0% (95% CI, −11% to 12%), and 2% (95% CI, −10% to 16%), respectively.

There was no trend in the effect of vitamin E or beta carotene on the coronary end points in relation to the duration of supplementation (**Table 3**). Likewise, 1-year incidence of major coronary events was similar after follow-up visits at which skin yellowing was reported compared with those visits without such a report. These analyses are based, however, only on active participants during the study and not on the intention-to-treat principle.

The effect of beta carotene supplementation on major coronary events and fatal coronary heart disease was different between men with a medical history of angina pectoris at baseline (relative risk, 0.74 and 0.64) and those without this history (relative risk, 1.05 and 1.09) (*P* for interaction, .02 and .01, respectively). Vitamin E supplementation had a different effect on major coronary events among men with a history of diabetes (relative risk, 0.69) compared with those without diabetes (relative risk, 0.98) (*P* for interaction, .04). No other interactions with baseline factors were observed.

The incidences of major coronary events were not related to serum alpha tocopherol or beta carotene response to supplementation. Quintiles of serum alpha to-

Table 1. Baseline Characteristics of the Men by Supplementation Group in the ATBC Study*

Characteristics	Median or Proportion			
	Vitamin E (n = 6820)	Vitamin E and Beta Carotene (n = 6781)	Beta Carotene (n = 6821)	Placebo (n = 6849)
Age, y	56.9	57.1	57.0	56.8
Serum total cholesterol, mmol/L (mg/dL)	6.13 (237)	6.17 (239)	6.13 (237)	6.14 (237)
Serum HDL cholesterol, mmol/L (mg/dL)	1.12 (43)	1.12 (43)	1.13 (44)	1.13 (44)
Systolic blood pressure, mm Hg	140	140	140	140
Diastolic blood pressure, mm Hg	88	88	88	88
Cigarettes smoked per day	20	20	20	20
Years of smoking	36	36	36	36
Body mass index, kg/m²†	25.9	26.0	25.9	25.9
Use of alcohol, g/d	11.4	11.1	11.0	11.0
History of angina pectoris, %	5.4	5.2	5.0	5.2
History of diabetes, %	3.7	4.3	4.3	3.7
Leisure exercise ≥3 times per week, %	19.4	19.8	19.2	19.1

*ATBC Study indicates Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; HDL, high-density lipoprotein.
†Body mass index is measured as the weight in kilograms divided by the square of the height in meters.

Table 2. Incidence (per 1000 Person-years) and Relative Risk (RR) of Primary Major Coronary Events Among Men Without Prior Myocardial Infarction by Supplementation Group in the ATBC Study*

Coronary Event	Vitamin E	Vitamin E and Beta Carotene	Beta Carotene	Placebo	P
All cases					
No. of cases	519	511	547	534	
Incidence	13.30	13.16	14.01	13.59	.75
RR (95% CI)	0.98 (0.87-1.10)	0.97 (0.86-1.09)	1.03 (0.91-1.16)	1.00	
Nonfatal myocardial infarction					
No. of cases	307	289	312	296	
Incidence	7.87	7.44	7.99	7.54	.79
RR (95% CI)	1.04 (0.89-1.22)	0.99 (0.84-1.16)	1.06 (0.90-1.24)	1.00	
Fatal coronary heart disease					
No. of cases	212	222	235	238	
Incidence	5.43	5.72	6.02	6.06	.63
RR (95% CI)	0.90 (0.75-1.08)	0.94 (0.79-1.13)	0.99 (0.83-1.19)	1.00	

*ATBC Study indicates Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI, confidence interval.

copherol concentrations after 3 years of supplementation (quintile cut points: 33.1, 38.0, 42.6, and 48.9 mg/L) corresponded to adjusted relative risks of subsequent major coronary events of 1.00 (reference), 1.18, 1.14, 1.25, and 1.18, respectively (*P* for trend, .42). For quintiles of serum beta carotene concentrations after beta carotene supplementation (3.00, 4.74, 6.33, and 8.34 µmol/L) the relative risks were 1.00, 0.88, 0.87, 0.77, and 0.92, respectively (*P* for trend, .44). Analysis of the change in serum concentration from baseline gave similar results.

Baseline dietary intake of vitamin E or beta carotene was not associated with the subsequent risk of major coronary events. The same was true for baseline serum alpha tocopherol level but baseline serum beta carotene concentration was inversely associated with the risk of death due to coronary disease (**Table 4**).

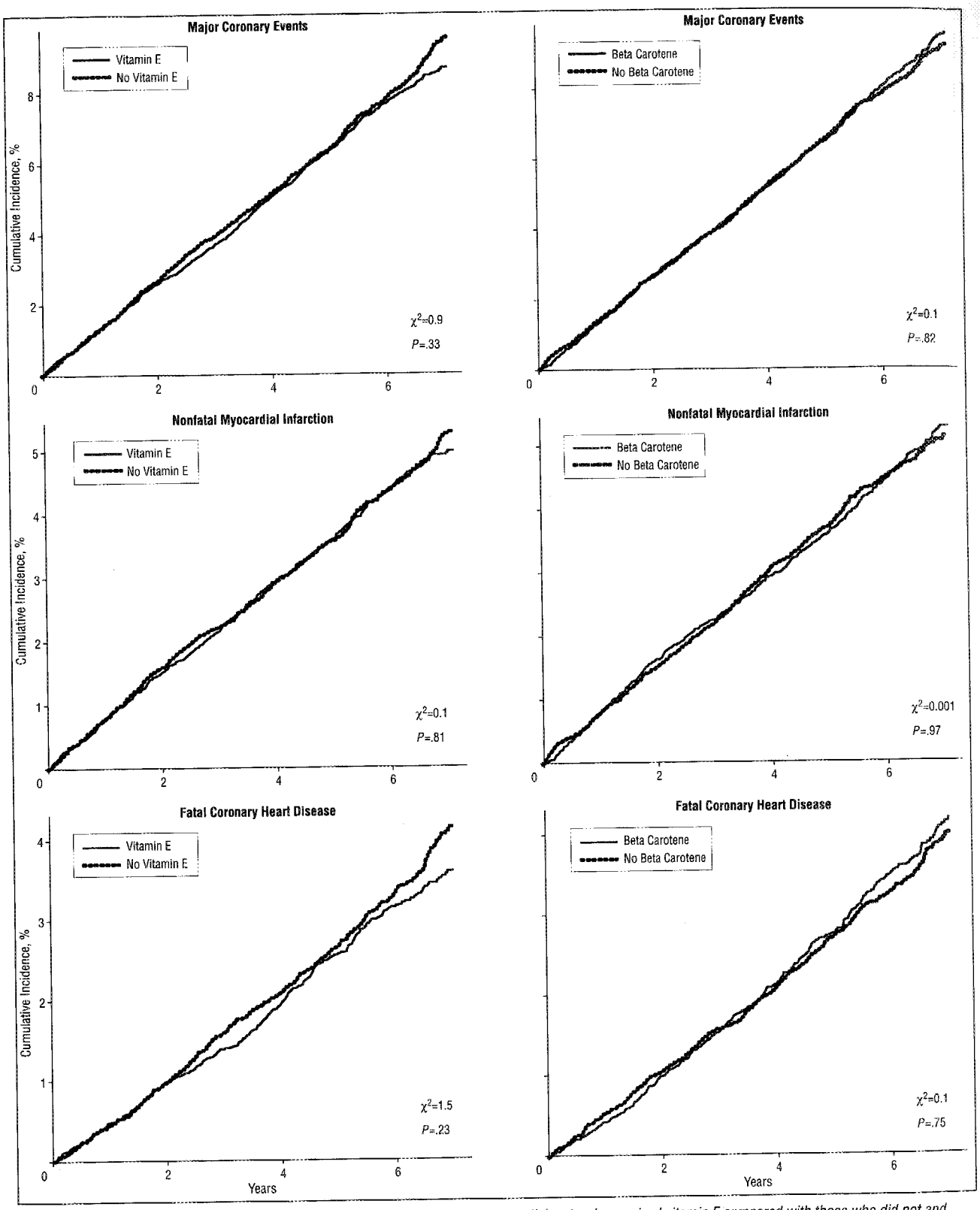
COMMENT

We examined the effect of 6 years of supplementation with vitamin E and beta carotene on major coronary events among men who had no medical history of myocardial infarction. Neither agent affected the incidence of nonfatal myocardial infarction. Vitamin E supplementation resulted in a nonsignificant 8% reduction in deaths due to coronary disease. Deaths resulting from coronary heart disease were not affected by beta carotene supplementation.

The primary analysis of the ATBC Study data demonstrated that beta carotene supplementation increased total mortality by 8%.[6] This resulted in part from increased ischemic heart disease. Further analyses revealed that this increase in deaths from coronary heart disease occurred among men who initially reported a history of myocardial infarction.[14]

Bias is an unlikely explanation for our results. At baseline the intervention groups were balanced with respect to all cardiovascular risk factors. The rate of self-reported skin yellowing, a potential breaker of double-blindness among men receiving beta carotene, was moderate and not related to coronary end points.

The hypothesis that antioxidants prevent coronary heart disease comes from the observed role of



Kaplan-Meier estimates of the incidences of primary major coronary events among participants who received vitamin E compared with those who did not and among participants who received beta carotene compared with those who did not. Results of the log-rank test for major coronary events are presented in the Figure.

oxidized low-density lipoprotein in atherogenesis. In vitro studies of serum from subjects receiving vitamin E or beta carotene supplements have shown that vitamin E but not beta carotene prolongs the copper- or iron-induced oxidation time of low-density lipoprotein.[15,16] Vitamin E seems to affect low-density lipoprotein oxidation at low dosages, 25 to 50 mg/d, but maximum influence is provided by doses up to 400 to

Table 3. Relative Risk* of Primary Major Coronary Events During the Next 12 Months Following Different Durations of Supplementation

Duration of Supplementation, y	No. of Men Still Taking Supplements	Vitamin E vs No Vitamin E			Beta Carotene vs No Beta Carotene		
		Major Coronary Events	Nonfatal Myocardial Infarction	Fatal Coronary Heart Disease	Major Coronary Events	Nonfatal Myocardial Infarction	Fatal Coronary Heart Disease
0	27 271	1.03	1.00	1.08	0.92	1.00	0.79
1	24 233	0.93	0.93	0.93	1.05	1.01	1.12
2	22 450	0.86	1.05	0.64†	0.92	0.81	1.10
3	21 484	1.06	1.10	1.00	0.87	0.77	1.07
4	20 111	1.06	0.98	1.17	1.04	1.00	1.10
5	15 531	0.91	0.92	0.90	1.17	1.13	1.21
6	9386	0.71	0.78	0.63	1.00	1.10	0.87
7	3093	1.49	1.13	2.13	1.00	0.98	1.09

*Adjusted for age, cigarettes smoked per day, years smoking, serum total and high-density lipoprotein cholesterol levels, systolic blood pressure, body mass index (measured as the weight in kilograms divided by the square of the height in meters), alcohol intake, leisure-time physical activity, and history of angina pectoris and diabetes; all measured at baseline.

†95% Confidence interval, 0.43 to 0.94. The 95% confidence intervals of all other relative risks include unity.

Table 4. Relative Risk* and 95% Confidence Intervals of Primary Major Coronary Events in the Quintiles of Baseline Serum Vitamin E and Beta Carotene in the Placebo Group

Quintile Ranges, μmol/L	Major Coronary Events	Nonfatal Myocardial Infarction	Fatal Coronary Heart Disease
	Vitamin E		
≤21.6	1.0	1.0	1.0
21.7-24.9	0.77 (0.55-1.06)	0.70 (0.45-1.09)	0.86 (0.53-1.39)
25.0-28.0	0.95 (0.69-1.31)	0.99 (0.65-1.51)	0.89 (0.54-1.46)
28.1-32.3	0.88 (0.63-1.22)	0.83 (0.54-1.28)	0.94 (0.57-1.56)
≥32.4	0.99 (0.71-1.38)	0.78 (0.49-1.23)	1.34 (0.81-2.20)
	P = .65	*P* = .52	*P* = .15
	Beta Carotene		
≤0.18	1.0	1.0	1.0
0.19-0.26	0.83 (0.62-1.10)	0.90 (0.60-1.35)	0.76 (0.51-1.15)
0.27-0.36	0.88 (0.66-1.17)	1.04 (0.70-1.55)	0.73 (0.48-1.12)
0.37-0.53	0.81 (0.60-1.09)	1.12 (0.76-1.66)	0.50 (0.31-0.81)
≥0.54	0.69 (0.50-0.94)	0.75 (0.48-1.15)	0.64 (0.41-1.00)
	P = .03	*P* = .47	*P* = .02

*Adjusted for age, cigarettes smoked per day, years smoking, serum total and high-density lipoprotein cholesterol levels, systolic blood pressure, body mass index (calculated as the weight in kilograms divided by the square of the height in meters), alcohol intake, leisure-time physical activity, and history of angina pectoris and diabetes; all measured at baseline.

800 mg.[17,18] On the other hand, studies of peroxidase-induced low-density lipoprotein oxidation suggest that the presence of small amounts of vitamin E enhances the rate of oxidation, and higher concentrations are needed to inhibit propagation of oxidation.[19] Beta carotene again may reduce the ability of arterial wall smooth muscle and endothelial cells to oxidize low-density lipoprotein.[20] Since the mechanism of in vivo oxidation of low-density lipoprotein is pending at present, it is not yet possible to estimate the roles and optimal doses of vitamin E or beta carotene for in vivo low-density lipoprotein oxidation. In our study the mean level of serum alpha tocopherol rose from 26.7 to 40.2 μmol/L among men who received vitamin E supplements, whereas in the Cambridge Heart Antioxidant Study[8] the level rose from 34.2 to 51.1 μmol/L, with daily vitamin E supplementation of 400 IU.[8]

An acute myocardial infarction develops when an atheromatous plaque disrupts and the exposed vessel wall and plaque constituents attract platelets, leading to the formation of an obstructive thrombus. The development of atherosclerosis is a prolonged process, and it may be argued that 6 years of supplementation has little effect on subjects with atherosclerotic coronary arteries who are exposed to a median of 36 years of smoking. However, administration of a lipid-lowering drug (pravastatin sodium) to men with moderate hypercholesterolemia and no history of myocardial infarction resulted in a reduction of the incidence of myocardial infarction and death from coronary heart disease already within the first year of treatment.[21] Our finding of new angina pectoris cases in men free of coronary heart disease at baseline[22] speaks for progression of atherosclerosis and thus also for the possibility of even short-term supplementation to modify the outcomes of coronary atherosclerosis. We

did not observe even a trend toward decreased risk of major coronary events when subjects used supplements for a longer period.

The results of previous controlled trials using vitamin E or beta carotene are inconsistent. In the Physicians' Health Study[5] in which more than 22 000 apparently healthy US male physicians took either beta carotene, 50 mg, or placebo every second day for 12 years, beta carotene had no effect on the incidence of coronary heart disease. The Beta-Carotene and Retinol Efficacy Trial,[7] interrupted because of an increase in lung cancer incidence and total mortality among 17 000 subjects who received a supplement of a daily combination of beta carotene (30 mg) and retinol (25 000 IU), showed a 28% increase in cardiovascular mortality; however, no information is available to estimate the influence of baseline coronary morbidity.

The effect of antioxidants in patients with established ischemic heart disease has been reported from 3 controlled trials. In the Physicians' Health Study,[23] a subgroup of 333 men with baseline evidence of coronary heart disease other than myocardial infarction experienced a 51% initial reduction in major coronary events, but a recent abstract reported reduction in myocardial infarctions but more deaths due to cardiovascular disease with beta carotene supplementation in this small subgroup.[24] In the Cambridge Heart Antioxidant Study,[8] 2002 patients with angiographically proven coronary atherosclerosis were given a supplement of vitamin E at daily doses of 400 or 800 IU for an average of 17 months. Vitamin E supplementation reduced the risk of nonfatal myocardial infarction by 77% (14 vs 41 patients) but there were 29% more deaths (36 vs 26 subjects), including more fatal myocardial infarctions in the group who received vitamin E supplements.[8] Among the 1862 ATBC Study participants with a history of myocardial infarction, both vitamin E and beta carotene and their combination decreased the incidence of nonfatal myocardial infarction compared with the placebo group (14%-38%), but increased the incidence of fatal coronary heart disease (33%-75%).[14]

Use of antioxidant supplements has been associated with reduced risk of coronary heart disease in observational studies. In the Health Professionals Follow-up Study,[3] the relative risk for major coronary events in men taking at least 100 IU/d of vitamin E supplements for 2 or more years was 0.63 (95% CI, 0.47-0.84) compared with men who did not take vitamin E supplements. In the Nurses' Health Study,[4] the corresponding relative risk for nonfatal myocardial infarction and death due to coronary heart disease was 0.52 (95% CI, 0.34-0.80). These findings do not, however, provide conclusive evidence that supplemental vitamin E reduces risk of coronary heart disease, since lifestyle and dietary patterns probably differ significantly between subjects who use supplemental antioxidants and those who do not. It is also notable that in the Health Professionals Follow-up Study,[3] total vitamin E intake (including supplements) of more than 25 IU/d was associated with a reduced risk of major coronary events (relative risk, 0.71; 95% CI, 0.54-0.92) compared with the total intake of less than 7 IU/d.

We found no consistent association between baseline dietary intakes and serum levels of vitamin E and beta carotene and the incidences of major coronary events in the placebo group; only serum beta carotene levels were inversely associated with deaths from coronary heart disease. This is in keeping with the inconsistent results of the few studies published so far. In the Health Professionals Follow-up Study[3] and the Nurses' Health Study,[4] dietary vitamin E intake was not associated with the risk of major coronary events. In the Health Professionals Follow-up Study, carotene intake was inversely associated with the risk of major coronary disease among current smokers and former smokers but not among those who had never smoked. In the Iowa Women's Health Study,[25] dietary vitamin E intake was inversely associated with the risk of death from coronary heart disease but no association was observed for dietary carotenoids. In a prospective cohort study in Finland,[26] in which more than 5000 men and women aged 30 to 69 years were followed up for a mean of 14 years, a significant inverse association was observed between dietary intake of vitamin E and coronary mortality in both men (P for trend, .07) and women (P for trend, $<.01$) but no association was found between dietary intake of carotenoids and deaths from coronary heart disease. Other smaller observational studies have found either moderate inverse or no association between vitamin E and beta carotene intake and the risk of coronary heart disease.[27] The lack of consistency in these studies suggests that other compounds in food rich in vitamin E or beta carotene are probably more important factors in the pathogenesis of coronary heart disease. On the other hand, the narrow range of intakes and the high intercorrelations between individual dietary antioxidants may have attenuated the effects of vitamin E and beta carotene.

The prevailing hypothesis by which antioxidants may contribute to the reduction of coronary heart disease is through protection of low-density lipoprotein from oxidative modification.[1] Vitamin E has, however, many other effects that may influence the pathogenesis of coronary heart disease. In vitro, it seems to modulate prostaglandin metabolism leading to inhibition of platelet aggregation, but in vivo it appears to inhibit platelet adhesion effectively and only weakly affects platelet aggregation.[28] Vitamin E also inhibits protein kinase C activity that can contribute to proliferation of smooth muscle cells[29] and endothelial dysfunction[30] in the arterial wall.

Considering the present results, it seems unlikely that beta carotene has a notable role in the prevention of coronary heart disease. On the other hand, the role of supplemental vitamin E is still open. We found only a modest, nonsignificant 8% decrease in deaths from coronary heart disease when a daily dose of 50 mg of vitamin E was administered. However, some studies suggest that supplemental vitamin E in dosages exceeding 100 mg/d may be more effective in the prevention of coronary heart disease. Ongoing studies address the effect of a higher vitamin E dose, and their results should be available within a few years. Until then, there are no grounds on which to recommend supplemental vitamin E to prevent coronary heart disease.

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